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THE REACTION OF 5,5-DIHALOBARBITURIC ACIDS WITH PYRIDINE[1, 2]

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A general synthesis of alloxazines and isoalloxazines by the condensation of *o*-phenylenediamines with 5,5-dihalobarbituric acids (rather than with alloxan, as in the conventional procedure) has been described by Tishler, Wellman, and Ladenburg (1), and pyridine was found to be a superior solvent for the reaction. In the course of a program directed towards the synthesis of condensed pteridine systems, we attempted a similar condensation between a number of 4,5-diaminopyrimidines and 5,5-dihalobarbituric acids, also in the presence of pyridine. We soon discovered that, regardless of the 4,5-diaminopyrimidine employed, the reaction product was the same in each case, and it was easily demonstrated that this product resulted from the reaction of the 5,5-dihalobarbituric acid with pyridine. This paper reports the results of our efforts leading to the elucidation of the structure of this compound.

The reaction product (henceforth designated I) was readily obtained by heating a mixture of 5,5-dichloro- or 5,5-dibromo-barbituric acid in pyridine for several hours, and was best purified by dissolution in dilute alkali followed by acidification. It was thus obtained as a bright yellow, crystalline solid which was completely insoluble in organic solvents, including boiling dimethylformamide, and which did not melt or darken below 360°. The compound did not contain halogen; elementary analysis led to the empirical formula $C_9H_7N_3O_3$, indicating that I was formed from one mole of 5,5-dihalobarbituric acid and one mole of pyridine with accompanying loss of halogen.

Methylation of I either with diazomethane in ether suspension or with dimethyl sulfate and alkali gave a compound, $C_{11}H_{11}N_3O_3$, (II), m.p. 304–306°, which was identical with the product of the reaction of 1,3-dimethyl-5,5-dichloro- (or dibromo-)barbituric acid with pyridine. It was thus apparent that I possessed an intact pyrimidine ring and that the site of attachment of pyridine to the pyrimidine ring was probably at position 5. The presence of an intact pyridine ring in I was demonstrated by the isolation of pyridine (as its picrate) from a reaction which involved heating I in 20% sodium hydroxide for 30 hours (ammonia was evolved) followed by acidification and addition of zinc dust. When the period of heating in alkali was extended to 70 hours and the reaction mixture then neutralized, *glycine* and *acetaldehyde* (as its 2,4-dinitrophenylhydrazone) were isolated. Therefore, pyridine must have been present in I in the form of a

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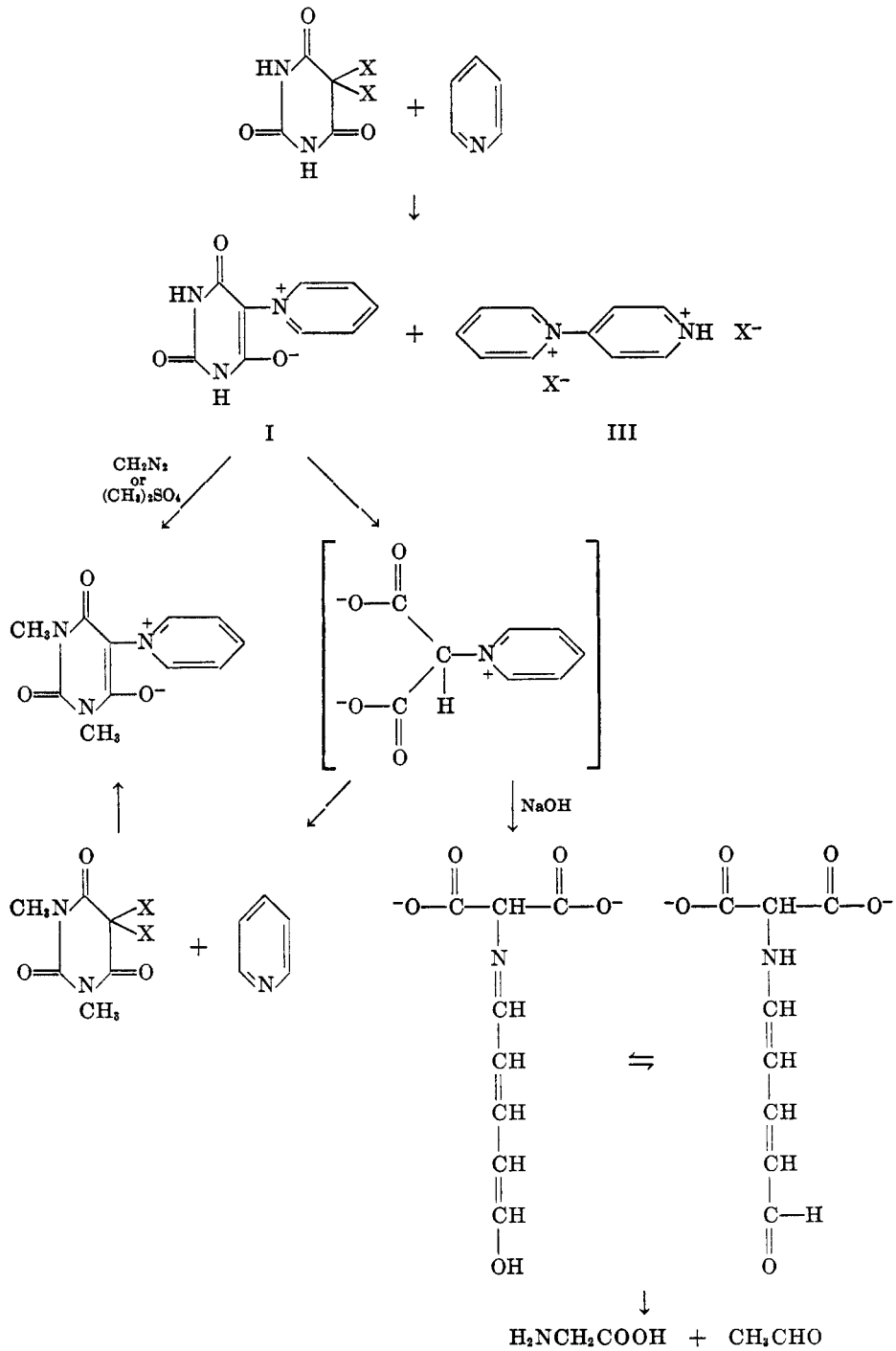

FIGURE 1

pyridinium salt, firmly bound to the pyrimidine ring. I thus appeared to be 1-[5-(2,4,6-trioxohexahydropyrimidyl)]pyridinium betaine (See Figure 1).

Strong support for this suggested structure for I is given by an examination of its ultraviolet absorption spectrum. I shows an absorption maximum in 0.1 *N* sodium hydroxide at 246 mμ, whereas the absorption maximum for an equimolar mixture of barbituric acid and pyridine is 256 mμ. The absorption maximum of pyridine itself is 252 mμ, while the absorption maximum of pyridine hydrobromide is 245 mμ. Thus, a maximum at 246 mμ is entirely consistent with the betaine structure I; the decrease in absorption maximum of I as compared with the equimolar mixture of pyridine and barbituric acid being due both to the presence in the former of the pyridinium ion rather than free pyridine, and to the dampening effect of the pyridinium ion on the barbiturate absorption, and the greater absorption maximum of I as compared with pyridinium hydrobromide being due to the increased extent of conjugation in I through the barbiturate ring.

When the filtrate of the original reaction mixture between 5,5-dibromobarbituric acid and pyridine was evaporated to dryness and the resulting brown solid was dried *in vacuo* and then sublimed, a colorless crystalline solid, m.p. 198–200°, (III), was obtained. It was evidently a complex of bromine and pyridine, since silver nitrate showed the presence of ionic bromine and pyridine was recovered from a basic solution of the compound. Conductivity measurements indicated the presence of four ions per molecule, while a molecular weight determination and elementary analysis led to the formula $C_{10}H_{10}Br_2N_2$. Heating the compound with water gave 4-pyridinol and pyridine hydrobromide. III was also obtained by the addition of a small amount of bromine to pyridine, removal of the excess pyridine by ether extraction and sublimation of the residue. III is thus 4-pyridyl-pyridinium bromide hydrobromide (See Figure 1), and it is curious that this simple complex has not been described previously.

Confirmation of this structure for the pyridine-bromine complex was obtained when the reaction mixture of pyridine and 5,5-dichlorobarbituric acid was shown to give 4-pyridyl-pyridinium chloride hydrochloride, identical with an authentic sample prepared by the action of thionyl chloride on pyridine.

Evidence bearing on a possible mechanism for the formation of I was obtained by examination of the behavior of other 5-substituted barbituric acids with pyridine. It was found that although 5-bromobarbituric acid did not react with pyridine, the ammonium salt of 5-bromobarbituric acid gave I in high yield. Although neither 5-nitrobarbituric acid nor its ammonium salt reacted with pyridine to give I, 5-bromo-5-nitrobarbituric acid and pyridine gave I in quantitative yield. A probable mechanism consistent with these observations is outlined in Figure 2 with 5,5-dibromobarbituric acid.

The reaction is initiated by nucleophilic attack by pyridine on bromine, displacing bromonium ion and giving rise to the anion of 5-bromobarbituric acid. A further nucleophilic attack of pyridine, this time on carbon to displace bromide ion, leads directly to I and 4-pyridyl-pyridinium bromide hydrobromide (III). The formation of I from 5-bromo-5-nitrobarbituric acid probably takes place by a similar mechanism, with the initial nucleophilic attack by pyridine resulting

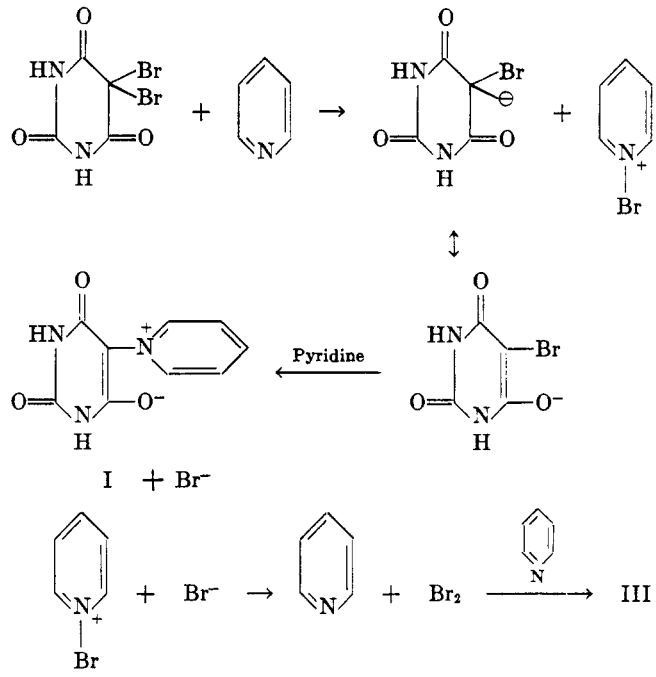

FIGURE 2

in the formation of the anion of 5-bromobarbituric acid, as before, and the displacement of nitronium ion. It seems clear that the reaction could not have proceeded in the reverse manner; *i.e.* with initial displacement of bromonium ion to give the anion of 5-nitrobarbituric acid, since the latter compound does not react with pyridine to give I.

The same mechanism must obtain with 1,3-dimethyl-5,5-dihalobarbituric acids and pyridine to give II, since the above observations were paralleled with the 1,3-dimethyl series; *i.e.*, although 1,3-dimethyl-5-bromobarbituric acid failed to react with pyridine, its ammonium salt gave II in high yield. II was also formed in high yield from 1,3-dimethyl-5-nitro-5-bromobarbituric acid and pyridine, while 1,3-dimethyl-5-nitrobarbituric acid failed to give II with pyridine.

It is of interest to point out that although a homolog of I was readily prepared from 5,5-dibromobarbituric acid and 4-picoline, no reaction took place with 2-picoline. Apparently the steric requirements of the *alpha*-methyl group are such as to prevent reaction at the hetero nitrogen atom.

EXPERIMENTAL[5]

1-[5-(2,4,6-Trioxohexahydropyrimidyl)]pyridinium betaine (I). (*A*). *From 5,5-dibromobarbituric acid and pyridine.* A mixture of 5.0 g. of 5,5-dibromobarbituric acid (2) in 50 ml.

[5] All melting points are uncorrected. Microanalyses were performed by Mrs. Lucy Chang, Mrs. Esther Fett, and Mr. Joseph Nemeth. The authors are indebted to Miss Helen Miklas and Mr. James Brader for the infrared absorption spectra determinations and to Miss Geraldine Meerman for the ultraviolet absorption spectra determinations.

of pyridine was heated under reflux for two hours, during which time the reaction mixture turned deep brown. The cooled reaction mixture was filtered and the collected solid was dissolved in 100 ml. of hot 0.5 *N* sodium hydroxide, treated with Norit, and filtered. The filtrate was added to 150 ml. of boiling 0.5 *N* acetic acid. Cooling caused the separation of a yellow crystalline solid which was separated by filtration and recrystallized as described above by dissolution in alkali followed by acidification; yield 4.40 g. (93.4%). It did not melt or darken below 360°.

Anal. Calc'd for $C_5H_7N_3O_3$: C, 52.2; H, 3.4; N, 20.5.

Found: C, 52.2; H, 3.4; N, 20.1.

(*B*). *From 5,5-dichlorobarbituric acid and pyridine.* From 5.0 g. of 5,5-dichlorobarbituric acid (3) and 50 ml. of pyridine there was obtained by the procedure outlined above 4.40 g. (86%) of I.

(*C*). *From the ammonium salt of 5-bromobarbituric acid and pyridine.* The ammonium salt of 5-bromobarbituric acid was prepared in 62% yield by treating 5,5-dibromobarbituric acid with an excess of concentrated ammonium hydroxide and recrystallizing the resulting solid from dilute ammonium hydroxide; m.p. 249–250° (dec.) (turns red at 130°).

Anal. Calc'd for $C_4H_6BrN_3O_3$: C, 21.4; H, 2.7; N, 18.8.

Found: C, 21.6; H, 2.7; N, 18.1.

Although the compound has been reported previously (2), no melting point was recorded.

I was obtained in 73% yield from the ammonium salt of 5-bromobarbituric acid and pyridine by heating the reactants under reflux for eight hours and isolating and purifying the product as described above.

(*D*). *From 5-bromo-5-nitrobarbituric acid and pyridine.* A solution of 0.5 g. of 5-bromo-5-nitrobarbituric acid (4) in 30 ml. of pyridine was heated under reflux for three hours and then cooled. The brown solid which separated was purified as described above to give 0.24 g. (58% yield) of I.

The products prepared by methods *A*, *B*, *C*, and *D* were shown to be identical by comparison of infrared spectra.

1-[5-(1,3-Dimethyl-2,4,6-trioxohexahydropyrimidyl)]pyridinium betaine (II). (*A*). *From I by methylation.* To a solution of diazomethane in ether (120 ml.) was added 3.00 g. of I and the mixture was shaken gently until nitrogen evolution ceased. The reaction mixture then was washed with water and the remaining solid was recrystallized from absolute ethanol to give 2.70 g. (79%) of II as a crystalline, yellow solid; m.p. 303–304°. It was readily purified by sublimation at 200°/10 mm.

Anal. Calc'd for $C_{11}H_{11}N_3O_3$: C, 56.6; H, 4.8; N, 18.0; M.W., 233.

Found: C, 56.8; H, 4.5; N, 17.7; M.W., 234.

II was also readily prepared from I by methylation with dimethyl sulfate. To a solution of 1.0 g. of I in 0.1 *N* sodium hydroxide was added 2.5 g. of dimethyl sulfate with constant shaking. The solution was kept basic by repeated additions of dilute sodium hydroxide. After the reaction mixture had become homogeneous, it was evaporated to dryness under reduced pressure and the resulting yellow residue was partially dissolved in chloroform. Addition of petroleum ether (90–120°) to the dried ($MgSO_4$) chloroform solution caused the separation of 1.02 g. (93%) of pure II, m.p. 303–304°, identical with the material prepared by methylation of I with diazomethane described above.

(*B*). *From 1,3-dimethyl-5,5-dibromobarbituric acid and pyridine.* A mixture of 5.0 g. of 1,3-dimethyl-5,5-dibromobarbituric acid (5) and 40 ml. of pyridine was heated under reflux for 1½ hours, during which time it turned reddish-brown in color. It then was evaporated to dryness under reduced pressure and the brown residue was extracted with chloroform. Addition of petroleum ether (90–120°) caused the separation of a yellow solid which was sublimed at 200°/10 mm. to give 3.5 g. (94%) of II, m.p. 304–306°.

(*C*). *From the ammonium salt of 1,3-dimethyl-5-bromobarbituric acid and pyridine.* A mixture of 1.00 g. of the ammonium salt of 1,3-dimethyl-5-bromobarbituric acid (2) and 25 ml. of pyridine was heated under reflux for a period of 8 hours and then worked up as described under *B* above to give 0.70 g. (75%) of II, m.p. 304–306°.

(*D*). *From 1,3-dimethyl-5-nitro-5-bromobarbituric acid and pyridine.* A mixture of 1.00 g. of 1,3-dimethyl-5-nitro-5-bromobarbituric acid (6) and 30 ml. of pyridine was heated under reflux for 12 hours and the resulting yellow-brown solid purified as described above to give 0.70 g. (85%) of II, m.p. 304–306°.

The products prepared by methods *A*, *B*, *C*, and *D* were shown to be identical by mixture melting point determinations and by comparison of infrared spectra.

Alkaline cleavage of I. A mixture of 3.00 g. of I, 100 ml. of water, and 15 g. of sodium hydroxide was heated under reflux for 30 hours. Ammonia was slowly evolved. After the reaction mixture had cooled, 20 ml. was removed and this portion was acidified with hydrochloric acid. Addition of zinc dust caused an exothermic reaction and evolution of carbon dioxide (calcium hydroxide test). The reaction mixture was then added to a boiling alcoholic solution of picric acid. Cooling gave the picrate of pyridine, m.p. 167–168°, identified by a mixture melting point determination with an authentic sample.

The remaining basic reaction mixture above was heated under reflux for an additional 40 hours. By this time ammonia evolution had ceased. The mixture was filtered, the filtrate was acidified with hydrochloric acid, and then was heated under reflux for 30 hours. During this time the evolved gases were passed through an alcoholic solution of 2,4-dinitrophenylhydrazine. A solid, m.p. 147–148°, which separated from this solution was identified as acetaldehyde 2,4-dinitrophenylhydrazone by a mixture melting point determination with an authentic sample.

The acidic reaction mixture then was evaporated to dryness under reduced pressure, and the solid residue was placed in a Soxhlet cup with 1.0 g. of sodium hydroxide and extracted with ethanol for 30 hours. Evaporation of the alcohol extract gave a solid, m.p. 235–238°, identified as glycine by a mixture melting point determination with an authentic sample and by paper chromatography.

Isolation and identification of 4-pyridyl-pyridinium bromide hydrobromide (III). The filtrate of the condensation reaction described above between 5,5-dibromobarbituric acid and pyridine (Preparation of I, Method A) was evaporated to dryness under reduced pressure. The resulting brown semi-solid was dried overnight in a vacuum-desiccator over calcium chloride and then sublimed at 130°/0.5 mm. to give a colorless solid, m.p. 198–200°. An identical compound (as shown by a mixture melting point determination and by comparison of infrared spectra) was prepared by adding 3 ml. of bromine to 50 ml. of pyridine, allowing the mixture to stand at room temperature overnight, and then extracting the excess pyridine with ether and subliming the dried residue.

Anal. Calc'd for $C_{10}H_{10}Br_2N_2$: C, 37.5; H, 3.9; N, 8.6; M.W., 318.
Found: C, 37.7; H, 3.7; N, 8.9; M.W., 328.

The product formed a *picrate*, m.p. 224–226° and contained ionic bromine (silver nitrate test). It was hydrolyzed as follows: A mixture of 2.0 g. of the compound in 50 ml. of water was heated under reflux for 80 hours and then evaporated to dryness under reduced pressure. The residue was partially soluble in water. Recrystallization of the water-insoluble portion from alcohol-chloroform gave 4-hydroxypyridine monohydrate, m.p. 92–93°; benzoyl derivative, m.p. 81–83°. Evaporation of the aqueous filtrate above gave pyridine hydrobromide, m.p. 215–218°, identical with an authentic sample.

Isolation and identification of 4-pyridyl-pyridinium chloride hydrochloride. The filtrate of the condensation reaction described above between 5,5-dichlorobarbituric acid and pyridine (preparation of I, Method *B*) was evaporated to dryness under reduced pressure and the brown semi-solid was dried in a vacuum desiccator and then sublimed at 140°/0.5 mm. to give a colorless solid, m.p. 173–175°. No depression in melting point was observed upon admixture with an authentic sample of 4-pyridyl-pyridinium chloride hydrochloride, prepared by the action of thionyl chloride on pyridine (7).

4-Methyl-1-[5-(2,4,6-trioxohexahydropyrimidyl)]pyridinium betaine. A suspension of 5.0 g. of 5,5-dibromobarbituric acid in 35 ml. of 4-picoline was heated under reflux for two hours, during which time the reaction mixture turned reddish-brown. Addition of 50 ml. of water to the cooled reaction mixture caused the separation of a brown solid which was collected by filtration and dissolved in 25 ml. of 0.1 *N* sodium hydroxide. Treatment of

this solution with charcoal followed by acidification of the filtrate with hot dilute acetic acid gave 1.33 g. (33%) of a silver-yellow crystalline solid which did not melt or change color below 360°.

Anal. Calc'd for $C_{10}H_{10}N_2O_3$: C, 54.8; H, 4.1; N, 19.2.
Found: C, 54.6; H, 4.1; N, 18.9.

SUMMARY

The reaction of 5,5-dichloro- or 5,5-dibromo-barbituric acid with pyridine has been shown to give 1-[5-(2,4,6-trioxohexahydropyrimidyl)]pyridinium betaine (I) and 4-pyridyl-pyridinium chloride hydrochloride or 4-pyridyl-pyridinium bromide hydrobromide respectively. The structure of I has been confirmed by degradative studies and by several alternative syntheses. Several examples illustrating the generality of the reaction have been given and a mechanism for the conversion has been advanced.

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